NEW RESEARCH

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Effect of Gaboxadol on Patient-reported Measures of Sleep and Waking Function in Patients with Primary Insomnia: Results from Two Randomized, Controlled, 3-month Studies

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Objective: To evaluate the efficacy and safety of gaboxadol in the treatment of Primary Insomnia.

Methods: Two studies were performed in patients 18 to 65 years of age with Primary Insomnia. After a 7-day single-blind placebo run-in, patients were randomized to double-blind treatment with gaboxadol 15 mg ($N = 310$), 10 mg ($N = 308$), or placebo ($N = 309$) over 3 months in Study 1; and gaboxadol 15 mg ($N = 304$) or placebo ($N = 301$) over 12 months in Study 2. Treatment was administered at bedtime. The primary efficacy endpoints in each study were change from baseline in patient-reported total sleep time (sTST) and time to sleep onset (sTSO) at month 3. Safety was assessed primarily by adverse event reports.

Results: In Study 1, gaboxadol 15 mg significantly improved sTST (difference vs. placebo of 20.4 min, $p < 0.01$) and sTSO (difference vs. placebo of -9.8 min, $p < 0.05$) at 3 months, while gaboxadol 10 mg had no significant effects on these measures. In Study 2, gaboxadol 15 mg showed numerical superiority for improvements on sTST (difference vs. placebo of 14.5 min) and sTSO (difference vs. placebo of -4.9 min) at 3 months, but these differences were not significant. In both studies, there was evidence that the efficacy of gaboxadol was more pronounced in women than men. Gaboxadol was generally well tolerated over 3 months in Study 1, and over 12 months in Study 2.

Conclusion: Gaboxadol 15 mg showed variable efficacy on measures of sleep duration and onset at 3 months in adult patients with Primary Insomnia in these studies and appeared to be more effective in women than men. Gaboxadol 10 mg was not effective in these studies. (Clinical trial registration numbers: NCT00103818, NCT00095069)

Keywords: Gaboxadol, Primary Insomnia, sleep, GABA, selective extrasynaptic GABA_A agonist

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Insomnia is one of the most pervasive sleep problems, with approximately 30% of the general adult population reporting 1 or more symptoms of insomnia, and approximately 6% meeting diagnostic criteria such as DSM-IV.[1] The disorder is thought to be more common in women than men.[2] Pharmacological treatment of insomnia typically involves the use of benzodiazepines (e.g., triazolam) as well as non-benzodiazepine hypnotics acting at the benzodiazepine receptor site (e.g., zolpidem) and sedating antidepressants such as trazodone.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Gaboxadol is an investigational drug which potentially offers a new means of treating insomnia via direct and selective agonism of extrasynaptic GABAA receptors. The aim of these studies was to determine the efficacy of gaboxadol over 3 months in patients with primary insomnia.

Study Impact: Gaboxadol provided inconsistent effects on sleep onset and duration over 3 months, although there was a tendency for greater efficacy in women than men. These data highlight the importance of looking at gender effects in hypnotic trials.

Gaboxadol is the first in a novel class of sleep medications which acts as a direct and selective agonist of extrasynaptic GABA_A receptors.[3] In addition to its unique mechanism of action, gaboxadol increases the amount of time spent in slow wave sleep.[4] Previous short-term studies demonstrated that gaboxadol improved measures of sleep maintenance and sleep onset over an initial 2 nights of treatment in patients with Primary Insomnia and was well tolerated.[5,6] Benefits have also been seen in 2 short-term studies in healthy volunteers using a model of transient insomnia[7,8] and most recently in a 2-week outpatient study[9] and two 30-night polysomnography studies.[10] Generally, gaboxadol doses of 10 to 20 mg appeared to be effective in the treatment of insomnia, with a 15-mg dose appearing to offer the most favorable benefit-risk profile in adults under 65 years of age.

The aim of the present 2 large studies was to determine the longer term efficacy of gaboxadol when given over periods of 3 months, and to determine the long-term tolerability of gaboxadol over periods of up to 12 months. Gaboxadol is no longer in clinical development for the treatment of insomnia based on an assessment of its overall clinical profile in phase 3 trials, including those reported here, which suggested limited or variable efficacy, and also the occurrence of psychiatric side effects at supra-therapeutic doses in an abuse liability study involving drug abusers.[11,12]

In addition to evaluating gaboxadol response in the overall population, we also explored possible sex differences in therapeutic response. The topic of possible sex differences in GABA receptor pharmacology,[13] and in neuroscience[14] and medicine in general,[15] has received increasing attention in recent years. Sex differences in treatment response have been reported for a number of conditions.[16] For example, the 5-HT$_3$ receptor antagonist alosetron appears to be more effective in women than men for the treatment of irritable bowel syndrome.[17] A similar finding of greater efficacy in women than men has been noted for antiretroviral therapy in HIV, although this is controversial.[18] Conversely, greater efficacy in men than women has been reported for propofol drug-induced analgesia and anesthesia.[19] The identification of sex differences in treatment response offers the potential for targeting therapeutic intervention at specific subgroups, with the possible advantage of an improved benefit-risk profile.

With regard to sleep biology, there is evidence for sex differences in sleep architecture. For example, women have been reported to have greater sleep latency than men and to spend more time in slow wave sleep.[20-23] Spectral analysis of EEG data has also shown that women have higher power density in the low-frequency range during sleep.[24,25] Sex differences in sleep related autonomic and respiratory responses have also been reported.[26] Sex differences discovered during the development of a new hypnotic could have potentially important implications regarding its future clinical use.

METHODS

Design

Two parallel group, multicenter, outpatient, double-blind randomized clinical trials were performed. Each study involved a 1-week single-blind placebo run-in period, followed by a 3-month (Study 1) or 12-month (Study 2) randomized double-blind treatment period, and then a 1-week double-blind run-out period (to assess possible rebound insomnia and withdrawal effects). Study 1 (Merck Protocol 014) included gaboxadol 15 mg, gaboxadol 10 mg, and placebo treatment groups, and was conducted at 50 sites in the United States from February 2005 to August 2006. Study 2 (Merck Protocol 003) included gaboxadol 15 mg and placebo treatment groups and was conducted at 41 sites in the United States from October 2004 to February 2007. In both studies, the primary period for assessing efficacy was the initial 3 months of double-blind treatment. Study 2 included an additional 9-month extension of double-blind treatment in order to further evaluate the long-term safety of gaboxadol.

Patients

In both studies, women and men 18 to 65 years of age diagnosed as having Primary Insomnia $\geq$ 4 weeks duration were enrolled based on DSM-IV criteria.[27] In addition, patients met the following self-reported criteria: regular bedtime between 20:00 and 01:00, total sleep time (sTST) < 6 h on $\geq$ 4 nights per week for the past 4 weeks, and time to sleep onset (sTSO) $\geq$ 45 min on at least 4 nights per week for the past 4 weeks. Women were required to be postmenopausal or post surgical sterilization, or using a barrier method of contraception.

Patients with a history of a sleep disorder other than Primary Insomnia (e.g., narcolepsy, sleep apnea) were excluded as were patients with a history of transmeridian travel (across time zones) or shift work in the 2 weeks prior to the screening visit. Patients who had an active Axis I or II disorder other than Primary Insomnia, those with a history of bipolar or psychotic disorder, and those with a history of alcohol or drug abuse as defined in DSM-IV (unless they fulfilled DSM-IV criteria for sustained remission) were also excluded. Patients were not eligible if they had been taking any of the following medications within 2 weeks prior to the screening visit: hypnotics, melatonin, stimulants, diet pills, sedating antihistamines, nonprescription medications that could affect sleep (e.g., valerian), any central nervous system depressants, anxiolytics, benzodiazepines, antipsychotics, or antidepressants. Patients were also not eligible if they had been taking fluoxetine or depot neuroleptics within 4 weeks prior to screening or any investigational compound within 12 weeks.

All patients gave written informed consent and the study was approved by the ethics committee responsible for each participating site. Subjects were compensated for their participation.

Procedure

Patients attended a medical screening visit during which their demographic data; medical, psychiatric, sleep, and medication histories; and symptoms of Primary Insomnia according to the DSM-IV criteria[27] were recorded. Vital signs, ECG, blood biochemistry, hematology, and a urine analysis were carried out at the screening visit. Medical reviews and physical, neurological, and psychiatric examinations were performed.

Patients who satisfied entry criteria then entered a 1-week single-blind placebo run-in period during which they completed morning electronic diaries to assess their insomnia. Patients who reported sTST < 6 h and sTSO $\geq$ 45 min on a minimum of 4 of 7 morning diaries during the run-in period entered the 3-month double-blind treatment phase. In Study 1, patients were randomized to treatment with gaboxadol 10 mg, gaboxadol 15 mg, or placebo in a 1:1:1 ratio. In Study 2, patients were randomized to gaboxadol 15 mg or placebo in a 1:1 ratio. Treatments were provided as capsules to be taken orally at bedtime. During the double-blind treatment phase, patients completed electronic morning and evening diaries daily during the first 4 weeks of treatment to assess sleep effects. After the first 4 weeks of treatment, patients completed the electronic morning and evening diaries during weeks 8 and 12.

Following the 3-month double-blind treatment phase in Study 1, patients entered a 7-night double-blind run-out phase to assess possible rebound insomnia (an increase in sTST or sTSO relative to baseline) or withdrawal effects in which half the patients previously assigned to gaboxadol were switched to placebo and the remaining patients remained on gaboxadol; patients assigned to placebo remained on placebo. Following the 3-month double-blind treatment phase in Study 2, patients entered a 9-month double-blind safety extension, followed by the same 7-night double-blind run-out procedure as used in Study 1. Data from the 7-night double-blind run-out phases in each study are not discussed in this report, which focuses on the pre-specified primary and secondary endpoints; generally, no rebound insomnia or withdrawal effects were observed.

Adverse events were recorded throughout the study and were rated by the investigator, while still blinded, with regard to severity and likelihood of being drug related. Vital signs, ECGs, routine laboratory assessments, and physical examinations were performed at regular intervals.

The allocation schedule for treatment assignment was computer generated, using the clinical allocation schedule system at Merck Research Laboratories. Study supplies consisted of visually identical capsules provided in numbered bottles. Investigators used an interactive voice response system to determine which bottle number should be used for an individual patient. All study personnel, including investigators, study site personnel, patients, and Merck staff remained blinded to treatment allocation throughout the study. Unblinding took place after data collection was complete.

Patients were asked to limit alcohol to 2 drinks a day and avoid alcohol ≥ 3 hours before going to bed during the study. Patients were asked to limit caffeine consumption to 5 cups a day and to refrain from caffeine consumption after 16:00. Patients were also asked to refrain from napping for more than 1 hour per day.

Assessments

Patients completed a morning questionnaire, on an electronic diary, every day after their usual morning routine and within 1 hour of waking. The morning questionnaire assessed the following variables with respect to the previous night's sleep: time medication was taken, time to sleep onset, number and duration of nocturnal awakenings, time of final awakening, presence/absence and quantification of premature awakening, time of waking in the morning, total sleep time, quality of sleep (visual analogue scale), and freshness on waking (visual analogue scale). The pre-specified primary measures assessed were sTST and sTSO, while number of awakenings (sNAW) was a pre-specified secondary endpoint. Patients also completed the Sheehan Disability Scale (SDS)[28] at the end of weeks 1, 2, 3, 4, 8, and 12. This consists of 3 questions on impairment of work, social life, and family life/home responsibilities. The recall period was 7 days, and higher scores (range = 0 to 30) indicate more impairment. The SDS was a pre-specified secondary endpoint.

In addition to the above assessments, an evening questionnaire was used to assess aspects of daytime function, Clinical Global Impressions were assessed at weeks 1, 2, 3, 4, 8, and 12, and other assessments such as the Profile of Mood States were administered at weeks 1, 4, and 12. These data are not presented in the present report, which focuses on the pre-specified primary and secondary endpoints.

Study Hypotheses and Statistical Power

In both studies, the primary hypotheses were that gaboxadol 15 mg would be superior to placebo as measured by change from baseline in mean sTST or mean sTSO at month 3. Secondary hypotheses were that gaboxadol 15 mg would be superior to placebo as measured by change from baseline in mean sNAW or mean SDS total score at month 3.

The studies were powered based upon estimates available at month 3 from a previous long-term study with another hypnotic.[29] Assuming a standard deviation of 70 min for the change from baseline in sTST at month 3, a planned sample size of 283 patients per group provided 86% power to declare a difference between gaboxadol 15 mg and placebo if the true underlying difference in the change from baseline in patient-reported total sleep time was 18 min (5% level, 2-sided test). Assuming a standard deviation of 55 min for the change from baseline in sTSO at month 3, a sample size of 283 patients per group provided 80% power to declare a difference between gaboxadol 15 mg and placebo if the true underlying difference in the change from baseline in sTSO was 13 min (5% level, 2-sided test).

Data Analysis

In both studies, a longitudinal data analysis model was used to assess efficacy based on a full-analysis-set population, which included all patients who took at least one dose of study medication and had at least one post-randomization assessment (and a baseline assessment for change from baseline analyses). The baseline value was the mean of the response variable during the 1-week single-blind placebo run-in phase. The value for month 3 was the mean of the response variable during the last week of month 3. For other time points, the value for each week/month was the average of the values over the last 7 days comprising that week/month. A longitudinal data analysis used a data-as-observed approach for handling missing data, which assumed that the missing data were missing at random. No imputation was made for missing data. The longitudinal data analysis model included factors for study center, time (as categorical variable), baseline value, treatment, and time-by-treatment interaction. An unstructured covariance was used for the within-subject correlation.

It was pre-specified that summary statistics would be calculated for the primary efficacy variables by sex. To further evaluate the consistency of treatment effect by sex, a post hoc longitudinal data analysis model was used for the primary endpoints in each study. Baseline weight and body mass index were also evaluated as continuous variables. The model included terms for baseline covariate, time (categorical variable), treatment, time-by-treatment interaction, and time-by-treatment-by-baseline factor interaction. In addition to the separate analyses for each study, a post hoc integrated analysis was performed, in which gaboxadol and placebo data from both studies at month 3 was pooled. An additional term for study was included in the model for the integrated analysis. A treatment-by-baseline-factor interaction was considered significant at the $\alpha = 0.10$ level. The data were also assessed by plotting the estimate of the difference in least square means (with 95% confidence intervals) between gaboxadol and placebo. Because gaboxadol 10 mg was not effective and was included in only 1 of the studies, the present report focused on the 15-mg dose of gaboxadol for examining effects of baseline covariates.

In each study, to account for multiplicity related to there being 2 primary hypotheses, Hochberg's procedure at the 5% level was used. If at least one of the primary hypotheses was positive according to this procedure, then the secondary hypotheses were evaluated at the 5% level using Hochberg's procedure**.** The lower dose of gaboxadol (10 mg) was included in Study 1 primarily to help characterize the dose-response and safety of gaboxadol; therefore, in Study 1, only hypotheses that were positive for gaboxadol 15 mg (after multiplicity adjustment) were tested at the 5% level for gaboxadol 10 mg. In practice, this made no difference to the statistical significance for any of the comparisons in Study 1 but did influence the findings in Study 2.

The primary analysis of safety data in each study was based on adverse events occurring during the double-blind 3-month treatment period in Study 1 or the 12-month treatment period in Study 2. The population for safety analyses was the all-patients-as-treated set. All patients who took at least one dose of randomized study medication were included in the analysis. If a patient received incorrect therapy for the entire double-blind treatment period, then this patient was analyzed for safety in accordance with the actual treatment received. Data for categories of adverse events (e.g., discontinuation due to adverse event) were analyzed using Fisher's Exact test.

RESULTS

Patient Accounting and Baseline Characteristics

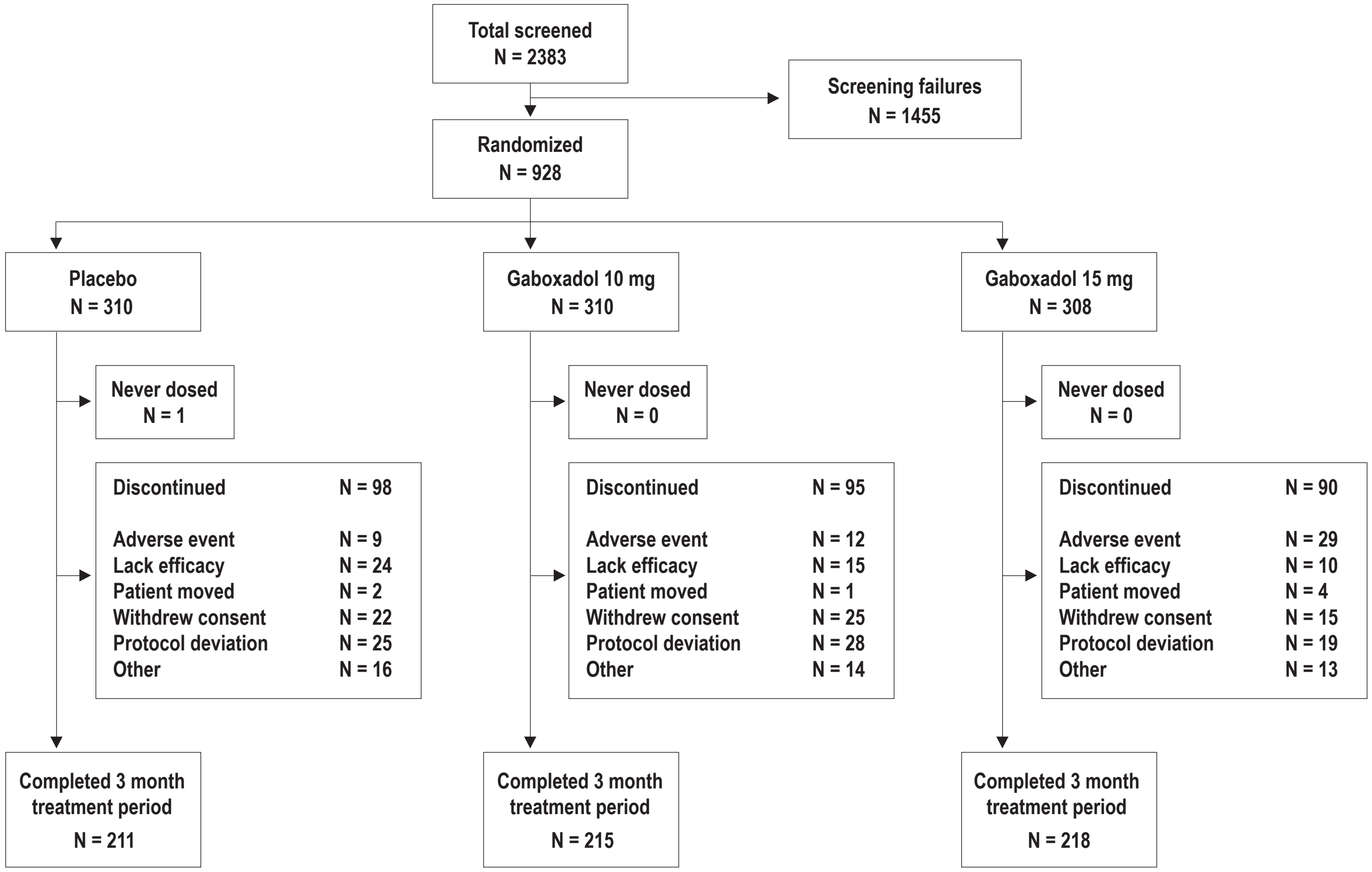
Study 1

Of the 2383 patients screened for inclusion in the study, 1455 were excluded during screening and not randomized. The main reasons for screening failure were not meeting sTST entry criteria (N = 466), not meeting sTSO entry criteria (N = 411), withdrawal of consent (N = 187), and having a positive urine drug screen (N = 163). A total of 928 patients were randomized, and 644 completed the 3-month double-blind treatment period (**Figure 1**). The overall numbers of patients discontinuing were similar between the groups, although the placebo group had the highest number of patients who discontinued due to lack of efficacy, and the gaboxadol 15 mg group had the highest number of patients who discontinued due to adverse events. Patient baseline characteristics and baseline values for efficacy endpoints are shown in **Table 1**. The mean age of patients was 43 years, approximately 65% were women, and the mean duration of the diagnosis of Primary Insomnia was 9 years. There was a slight sex imbalance between the treatment groups, with fewer women in the placebo group than either gaboxadol group. Also, patients in the placebo group had a slightly lower mean baseline score on the SDS. Otherwise, patient baseline characteristics and baseline values for efficacy endpoints were similar across treatment groups. Pooled across all treatment groups, baseline sTST was similar for women and men, while sTSO was slightly greater for women (mean sTST = 277.8 min in women and 279.8 min in men; mean sTSO = 102.6 min in women and 95.8 min in men).

Study 2

Of the 1558 patients screened for inclusion in the study, 950 were excluded during screening and not randomized. The main

Figure 1—Study 1 flowchart for the 3-month double-blind treatment period.



This was followed by a 7-night double-blind run-out period which is not shown.

reasons for screening failure were not meeting sTSO entry criteria (N = 299), not meeting sTST entry criteria (N = 295), withdrawal of consent (N = 121), and having a positive urine drug screen (N = 98). A total of 605 patients were randomized: 370 completed the primary 3-month double-blind treatment period used to evaluate efficacy, and 236 completed the entire 12-month treatment period used to evaluate safety (**Figure 2**). The overall numbers of patients discontinuing were similar between the groups, although the placebo group had the highest number of patients who discontinued due to lack of efficacy, and the gaboxadol 15 mg group had the highest number of patients who discontinued due to adverse events. Patient baseline characteristics and baseline values for efficacy endpoints are shown in **Table 1**. The mean age of patients was 45 years: approximately 58% were women, and the mean duration of diagnosis of Primary Insomnia was approximately 9 years. Patients in the placebo group had a slightly longer TSO at baseline compared with patients in the gaboxadol group. Otherwise, patient baseline characteristics and baseline values for efficacy endpoints were similar across treatment groups. Pooled across all treatment groups, baseline sleep appeared similar for women and men (mean sTST = 281.2 min in women and 281.7 min in men; mean sTSO = 95.5 min in women and 95.8 min in men).

Efficacy in Overall Population

Study 1

Summary statistics for the difference between gaboxadol and placebo in mean change from baseline score at month 3 (primary time point) are shown in **Table 2**. Data for week 1 are also shown in Table 2 to illustrate initial treatment efficacy. Gaboxadol 15 mg showed significant improvements on the sleep and daytime function measures at month 3 and week 1, whereas gaboxadol 10 mg showed significant improvements only at week 1 for sTST and sNAW.

Study 2

Summary statistics for the difference between gaboxadol 15 mg and placebo in mean change from baseline score at month 3 (primary time point) are shown in **Table 2**. Data for week 1 are also shown in **Table 2** to illustrate initial treatment efficacy. Based on the testing strategy to adjust for multiplicity, no significant differences were seen between gaboxadol 15 mg and placebo at month 3. However, nominally significant differences (p-values ≤ 0.05) for gaboxadol 15 mg vs. placebo were seen for sTST and sNAW at month 3, and for sTST, sNAW, and SDS total score at week 1.

Effect of Sex and Other Baseline Covariates

In both the individual studies, and in the 2 studies combined, the efficacy of gaboxadol 15 mg with respect to increasing sTST or decreasing sTSO appeared to be numerically larger in women than in men at month 3 (**Figure 3**). In the combined analysis of month 3 sTST data, the treatment-by-sex interaction showed a significant trend at the α-level of 10% (p = 0.060); no significant trends at month 3 were seen for treatment-by-weight (p = 0.693) or treatment-by-body mass index (p = 0.966) interactions. In the combined analysis of month 3 sTSO data, the treatment-by-sex interaction showed a significant trend at the α-level of 10% (p = 0.083). For sTSO, significant effects at month 3 were also seen for treatment-by-weight (p = 0.037) and treatment-by-body mass index (p = 0.016) interactions, with greater efficacy seen in those with lower weight/body mass. Since gender is correlated with the covariates of weight and body mass, additional analyses were conducted to gain insight into these interactions.

To further explore the sex difference in treatment effect of gaboxadol 15 mg, a multivariate analysis adjusting for the other baseline factors of weight and body mass index was performed. Since treatment-by-sex interactions were generally consistent at week 1 and month 3, and to use the largest possible dataset to investigate this issue, the analysis focused on week 1 data and

Table 1—Baseline characteristics of Primary Insomnia patients in Study 1 and Study 2

	Study 1			Study 2	
Demographics	**Placebo (N=309)**	**Gaboxadol 10 mg (N=310)**	**Gaboxadol 15 mg (N=308)**	**Placebo (N=301)**	**Gaboxadol 15 mg (N=304)**
Mean (SD) age, years	42.5 (12.1)	43.1 (11.9)	43.6 (11.2)	45.3 (12.0)	45.0 (11.5)
Mean (SD) weight, kg	76.4 (14.8)	76.6 (15.4)	76.6 (14.9)	77.1 (14.6)	77.0 (15.2)
Female, %	60.8	64.5	68.2	58.5	58.2
White, %	68.0	72.9	69.5	67.8	70.4
Mean (SD) diagnosis duration, years	8.8 (9.6)	8.7 (9.2)	8.7 (9.8)	9.4 (10.8)	9.4 (10.5)
Sleep[1]					
Mean (SD) sTST, min	278.0 (52.9)	279.4 (49.8)	278.0 (49.5)	280.9 (52.6)	281.9 (48.5)
Mean (SD) sTSO, min	99.0 (50.5)	98.4 (48.9)	103.2 (53.3)	98.0 (56.4)	93.3 (46.2)
Mean (SD) sNAW, n	2.1 (1.3)	2.0 (1.2)	2.2 (1.6)	2.2 (1.3)	2.1 (1.6)
Daytime Function[1]					
Mean (SD) SDS total score, 0=best, 30=worst	9.3 (7.8)	10.5 (8.1)	10.4 (7.8)	9.9 (7.9)	10.0 (7.6)

[1] Baseline = the last day of the single-blind run-in period

included data from 3 additional studies in Primary Insomnia patients between the ages of 18 and 65 years (Merck Protocols 004 and 040, and Lundbeck Protocol 99775). The combined studies had a total sample size of 1256 women (627 for gaboxadol 15 mg and 629 for placebo) and 725 men (363 for gaboxadol 15 mg and 362 for placebo). For sTST, the sex difference in efficacy of gaboxadol 15 mg remained significant at an α-level of 10% even after adjustment for main effects of weight and body mass index (all p-values ≤ 0.001), and adjustment for differential treatment effects of weight (p = 0.008) and body mass index (p = 0.002). For sTSO, the sex difference in efficacy of gaboxadol 15 mg remained significant at an α-level of 10% even after adjustment for main effects of weight and body mass index (all p-values ≤ 0.01), and adjustment for differential treatment effects of weight (p = 0.007) and body mass index (p = 0.002).

Safety

Study 1

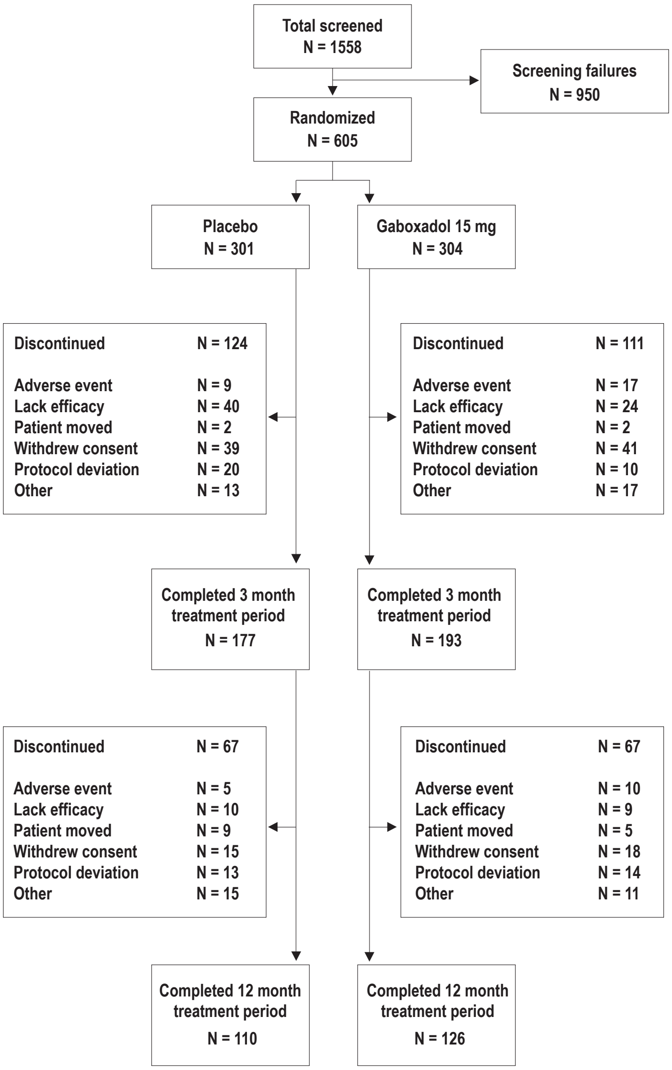
Gaboxadol 10 mg and 15 mg were generally well tolerated during the 3-month double-blind treatment period (**Table 3**). Significant differences in incidence rates between gaboxadol 15 mg and placebo were observed for the proportion of patients who reported an adverse event ($p < 0.05$) or who discontinued due to adverse events ($p < 0.001$). The most common adverse events in the gaboxadol 15 mg group were dizziness, nausea, and headache (**Table 3**). The most common adverse events in the gaboxadol 15 mg group leading to discontinuation were dizziness and headache. Most adverse events were judged to be mild or moderate in intensity and were relatively short in duration. No patients died during the study. Four patients, all in the gaboxadol 15 mg group and all women, had adverse events that were classified as serious. These consisted of anxiety, abnormal coordination, abnormal thinking, nausea and vomiting (1 patient), sedation (1 patient), chest pain (1 patient), and non-cardiac chest pain (1 patient). In all cases, patients recovered (with therapeutic intervention in some cases). All serious adverse events except chest pain (1 patient) were rated as drug related by the investigator. There were no clinically relevant differences between treatment groups in laboratory values, ECGs, vital signs, or neurological examinations.

For gaboxadol 15 mg, there was some evidence of a sex difference, in that a higher percentage of women than men had adverse events (61.0% vs. 44.9%), discontinuations due to adverse events (11.4% vs. 6.1%), and serious adverse events (1.9% vs. 0%). Exploratory analyses of selected specific adverse events for gaboxadol 15 mg suggested that women were more likely than men to experience dizziness (odds ratio for women vs. men = 2.33, p = 0.070).

Study 2

Gaboxadol 15 mg was generally well tolerated over the entire 12-month double-blind treatment period (**Table 3**). A significant difference between gaboxadol 15 mg and placebo was observed for the percentage of patients who reported an adverse event. The most common adverse events in the gaboxadol 15 mg group were dizziness, nausea, headache, nasopharyngitis, and upper respiratory tract infection (**Table 3**). The most common adverse events leading to discontinuation were dizziness and nausea. Most adverse events were judged to be mild or moderate in intensity and were relatively short in duration. No patients died during the study. Nine patients (6 women and 3 men) in the gaboxadol 15 mg had adverse events that were classified as serious vs. 3 patients (all women) in the placebo group. The serious adverse events in the gaboxadol group consisted of uterine leiomyoma (1 patient), anaphylactic shock (1 patient), pneumonia (1 patient), ECG poor R-wave progression (1 patient), spinal column stenosis (1 patient), dizziness (1 patient who took 30 mg), hypokalemia (1 patient), overdose (1 patient who took 60 mg; overdose was pre-specified as serious adverse event even though in this case the patient reported no symptoms), and basosquamous carcinoma (1 patient). In all cases, patients recovered (with therapeutic intervention in some cases). Two of the serious adverse events in the gaboxadol group were rated as drug related by the investigator (dizziness and ECG poor R-wave progression). There were no clinically

Figure 2—Study 2 flowchart for the 12-month double-blind treatment period.



This was followed by a 7-night double-blind run-out period which is not shown. Efficacy analyses were based on the first 3 months of the double-blind treatment period.

Table 2—Efficacy results at week 1 and month 3 (primary timepoint) in Primary Insomnia patients in Study 1 and Study 2 Difference (95% CI) between gaboxadol and placebo in mean change from baseline score

	Study 1				Study 2	
	Week 1		Month 3		Week 1	Month 3
Measure	**Gaboxadol 10 mg**	**Gaboxadol 15 mg**	**Gaboxadol 10 mg**	**Gaboxadol 15 mg**	**Gaboxadol 15 mg**	**Gaboxadol 15 mg**
Sleep						
N	299	288	190	185	289	183
sTST, min	13.1 (4.3, 21.9)**	21.7 (12.8, 30.6)***	3.7 (−9.3, 16.7)	20.4 (7.3, 33.5)**	13.8 (4.9, 22.7)*	14.5 (1.0, 27.9)[a]
sTSO, min	−5.3 (−11.3,0.7)	−10.0 (−16.1, −4.0)**	−3.3 (−10.6, 3.9)	−9.8 (−17.1, −2.5)*	−4.6 (−10.6, 1.5)	−4.9 (−12.6, 2.9)
sNAW, n	−0.1 (−0.3, −0.0)*	−0.2 (−0.3, −0.1)*	−0.1 (−0.2, 0.1)	−0.2 (−0.4, −0.1)*	−0.2 (−0.3, −0.1)*	−0.2 (−0.4, −0.0)[a]
Daytime Function						
N	283	282	210	216	289	203
SDS total score	−0.5 (−1.3,0.4)	−0.9 (−1.7, −0.0)*	−0.9 (−1.9, 0.1)	−1.9 (−2.9, −0.8)***	−0.9 (−1.7, −0.1)*	−1.0 (−2.1, 0.1)

*p ≤ 0.05, **p < 0.01, ***p < 0.001 vs. placebo. [a]nominal p-value < 0.05, but declared not significant according to the testing strategy to adjust for multiplicity.

Table 3—Summary of adverse events in Primary Insomnia patients during the 3-month treatment period in Study 1 and the 12-month treatment period in Study 2

	Study 1—3 months						Study 2—12 months			
	Placebo (N=309)		Gaboxadol 10 mg (N=310)		Gaboxadol 15 mg (N=308)		Placebo (N=301)		Gaboxadol 15 mg (N=304)	
Adverse event category	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
≥ 1 adverse event	138	44.7	140	45.2	172	55.8*	190	63.1	222	73.0*
≥ 1 serious adverse event	0	0.0	0	0.0	4	1.3	3	1.0	9	3.0
Discontinued due to adverse event	9	2.9	12	3.9	30	9.7***	16	5.3	27	8.9
Common adverse events (incidence ≥ 5% in any treatment group)										
Nausea	3	1.0	8	2.6	16	5.2	9	3.0	33	10.9
Upper respiratory tract infection	17	5.5	10	3.2	12	3.9	30	10.0	34	11.2
Dizziness	7	2.3	21	6.8	34	11.0	9	3.0	35	11.5
Headache	20	6.5	17	5.5	22	7.1	27	9.0	35	11.5
Nasopharyngitis	10	3.2	6	1.9	6	1.9	22	7.3	32	10.5

*p < 0.05, ***p < 0.001, vs. placebo (analysis based on estimate of risk difference vs. placebo for each category; the individual common adverse events were not analyzed)

relevant differences between treatment groups in laboratory values, ECGs, vital signs, or neurological examinations.

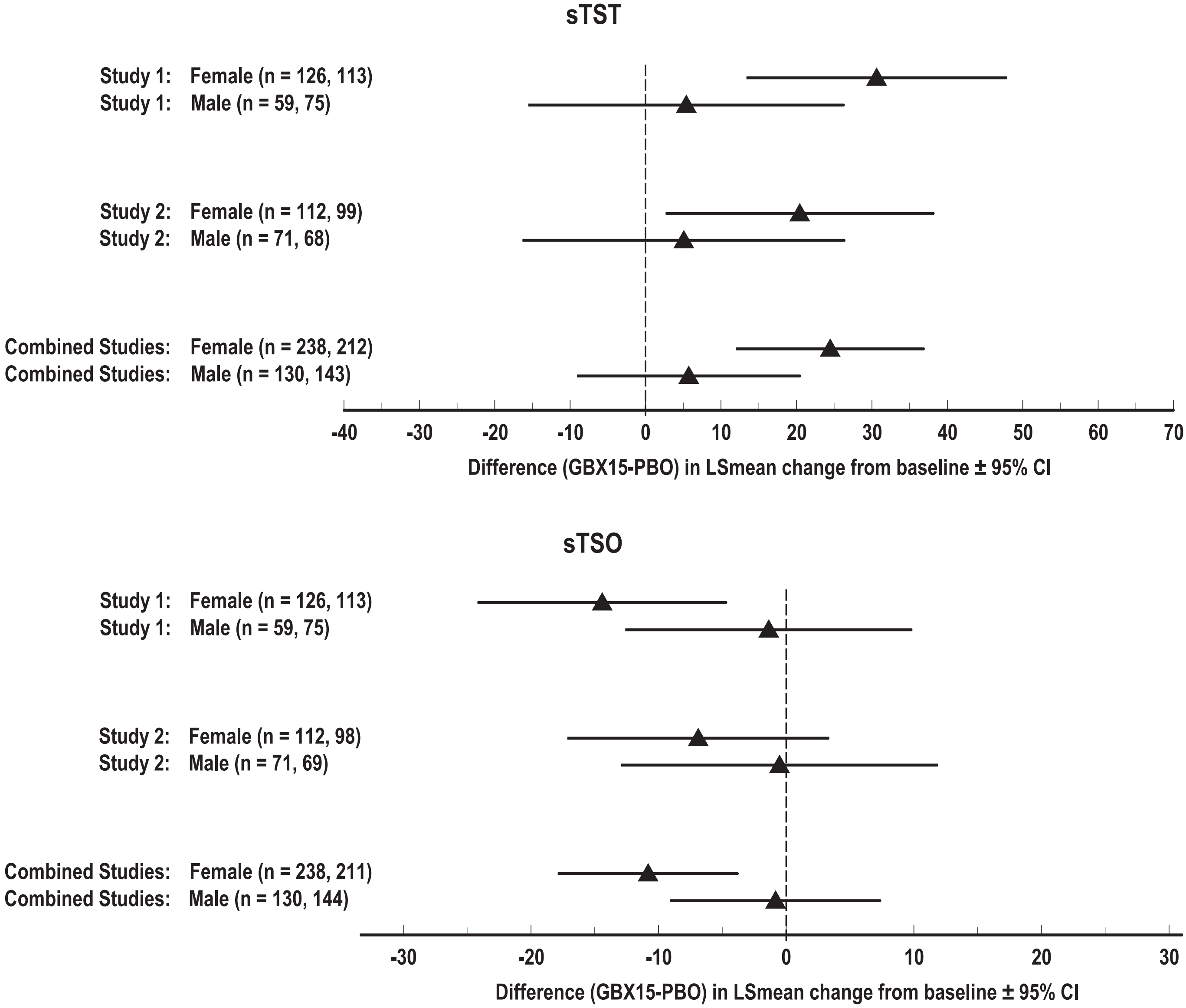
For gaboxadol 15 mg, there was some evidence of a sex difference, in that a higher percentage of women than men had adverse events (79.7% vs. 63.8%), discontinuations due to adverse events (9.0% vs. 0%), and serious adverse events (3.4% vs. 2.4%). Exploratory analyses of selected specific adverse events for gaboxadol 15 mg suggested that women were more likely than men to experience dizziness (odds ratio for women vs. men = 3.22, p = 0.008) and nausea (odds ratio for women vs. men = 4.59, p = 0.002).

DISCUSSION

In Study 1, nightly treatment with gaboxadol 15 mg over 3 months resulted in significant improvement in patient-reported measures of both sleep onset (sTSO) and sleep maintenance (sTST, sNAW) compared with placebo. The treatment effect of gaboxadol 15 mg on sleep onset and sleep maintenance was evident at week 1. Gaboxadol 15 mg also improved daytime functioning as measured by SDS at week 1 and month 3. Compared with placebo, treatment with gaboxadol 10 mg had no significant benefits on sleep onset, sleep maintenance, or daytime function at month 3. These findings are consistent with data from a previous 30-night polysomnography study which found that gaboxadol 15 mg, but not gaboxadol 10 mg, was effective in adult Primary Insomnia patients.[10]

Study 2 showed generally similar trends for improvements with gaboxadol 15 mg vs. placebo, but to a less consistent extent than in Study 1, and the results were nonsignificant according to the pre-defined testing strategy. The studies had identical inclusion criteria and similar designs. The lack of statistical significance in Study 2 was driven primarily by the failure to demonstrate an effect on sleep onset. This is in line with previous observations that

Figure 3—Effect of sex on gaboxadol 15 mg response for sTST and sTSO at month 3 in studies 1 and 2 and both studies combined.



n = x, y indicates the number of patients in the gaboxadol group (x), number of patients in placebo group (y). Values shown are the difference (gaboxadol 15 mg [GBX 15] minus placebo [PBO]) in least square mean change from baseline ± 95% confidence intervals. For sTST, values to the right of the vertical "0" line indicate greater improvement (i.e., increase in sTST) for gaboxadol 15 mg relative to placebo. For sTSO, values to the left of the vertical "0" line indicate greater improvement (i.e., reduction in sTSO) for gaboxadol 15 mg relative to placebo. The plots suggest that gaboxadol 15 mg was more effective in women than men.

gaboxadol's effects tended to be most consistent for sleep maintenance measures rather than sleep onset measures.[6,10] There was no clear reason for the generally reduced effects of gaboxadol in Study 2, compared to Study 1. Patient baseline characteristics and baseline scores on outcome measures were generally similar between the 2 studies. However, there was a somewhat lower percentage of women in Study 2 (58%) than Study 1 (65%), which may have contributed to the findings.

Because there have been some suggestions of sex differences in treatment response in previous gaboxadol clinical trials,[10] the present analyses examined this issue in greater detail in a post hoc manner. In both the individual studies, as well as in the 2 studies combined, there was a trend for the efficacy of gaboxadol 15 mg with respect to increasing sTST or decreasing sTSO to be larger in women than in men at month 3. In some cases, significant effects at month 3 were also seen for weight and body mass index, with greater efficacy seen in those with lower weight/mass. It is difficult to interpret these findings because the distribution of the other covariates differed between the 2 sexes, in that women had lower weight/body mass than men. However, in the multivariate analysis, the sex difference in gaboxadol 15 mg response remained even after adjustment for these other covariates. These data suggest that the observed sex difference in response might be indicative of a true biological difference and is not explicable solely in terms of weight/body mass differences between the sexes.

In support of this argument, sex differences in the effects of gaboxadol on EEG power spectra have been recently reported, with gaboxadol resulting in larger increases in delta and theta activity during sleep for women vs. men.[30] The present findings, and those of Dijk et al.[30] appear unlikely to be attributable to sex differences in pharmacokinetics; the pharmacokinetics of gaboxadol are generally similar in men and women, although plasma concentrations may be slightly higher in women.[31] Based on animal data, Dijk et al.[30] hypothesized that the sex difference in gaboxadol effects could be due to differences between males and females in number and distribution of $GABA_A$ receptor subtypes,[32] or an interaction between sex dependent neurosteroids and specific $GABA_A$ receptor subtypes.[33] Such explanations must be considered speculative at present.

With regard to safety, gaboxadol was well tolerated over 3 months in Study 1, and over 12 months in Study 2. In both studies, more patients reported adverse events on gaboxadol than placebo. The most common adverse events were dizziness and nausea, which tended to be short-lasting and of mild or moderate severity. There were more serious adverse event reports with gaboxadol vs. placebo but there was no clear pattern or single predominant cause for the adverse events. In both studies, there was some suggestion of a sex difference with women tending to report more adverse events or common adverse events than men. As for efficacy, this finding might be confounded by differences in weight/body mass between the sexes. A greater susceptibility to adverse effects in women has been suggested for some other hypnotic agents such as zolpidem.[34]

In summary, gaboxadol 15 mg provided inconsistent efficacy over 3 months in these studies, particularly with regard to sleep onset, while gaboxadol 10 mg was not effective. Gaboxadol 15 mg was generally well tolerated over periods of up to 12 months. There was evidence in a post hoc analysis of a possible sex difference in gaboxadol response with women showing greater efficacy than men but also a tendency to have an increased number of adverse events. The reason for this sex difference is unclear but the findings suggest that sex may be an important factor to take into account when investigating the effects of hypnotics.

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